UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

01/AUG/2008

MEMORANDUM

Subject:	Name of Pesticide Product:	Thiencarbazone-methyl Technical Herbicide
	EPA File Symbol:	264-RNAN
	DP Barcode:	D339738
	Decision No.:	378451
	Action Code:	R01
	PC Code:	015804 (Thiencarbazone-methyl)

From: Eugenia McAndrew, Biologist E McAndrew
Technical Review Branch
Registration Division (7505P) M Hasler

To: Hope Johnson, RM Team 25
Herbicide Branch
Registration Division (7505P)

Applicant: Bayer CropScience LP
P.O. Box 12014
2 T.W. Alexander Drive
Research Triangle Park, NC 27709

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Thiencarbazone-methyl	97.58
Inert Ingredient(s):	2.42
Total:	100.00%

ACTION REQUESTED: RM requests: "Bayer CropScience has submitted a new herbicide AI: thiencarbazone-methyl. This new AI is a Tri-Lateral Review with PMRA and the UK. The UK is the lead for the acute toxicology. This is the technical product: 264-RNAN. Enclosed are the acute toxicity studies (including some on metabolites), label and CSF."

BACKGROUND: Bayer CropScience LP has submitted seven acute toxicity studies to support the registration of the proposed product, Thiencarbazone-methyl Technical Herbicide, EPA File Symbol 264-RNAN: two acute oral, acute dermal, acute inhalation, primary eye irritation, primary skin irritation and dermal sensitization. The studies were conducted at Bayer HealthCare AG, PH-PD Toxicology International, 42096 Wuppertal, Germany and Bayer CropScience, France with assigned MRID numbers 470701-19, -22, -23, -24, 470702-03, -04 and -05. A CSF dated February 22, 2007 for a basic formulation is included in the submission. This new active ingredient is part of a tri-lateral review with Canada, the UK and the US. The UK conducted the primary review of the seven studies submitted for the technical in OECD format. The US and Canada performed secondary reviews.

Bayer has also submitted three acute oral studies conducted on metabolites N-desmethyl, carboxylic acid and sufonamide (MRIDs 47070120, 47070121 and 47070210) and acute dermal, primary eye irritation, primary skin irritation and dermal sensitization studies conducted on sulfonamide (MRIDs 470702-06, -07, -09 and -11).

RECOMMENDATIONS: The seven studies submitted to support the registration of the technical have been reviewed and are classified as acceptable.

The acute toxicity profile for Thiencarbazone Technical Herbicide, EPA File Symbol 264-RNAN, is as follows:

Acute oral toxicity	III	Acceptable	MRID 47070119
Acute oral toxicity	III	Acceptable	MRID 47070205
Acute dermal toxicity	III	Acceptable	MRID 47070122
Acute inhalation toxicity	IV	Acceptable	MRID 47070123
Primary eye irritation	IV	Acceptable	MRID 47070124
Primary skin irritation	IV	Acceptable	MRID 47070203
Dermal sensitization (guinea pig)	Neg.	Acceptable	MRID 47070204

The following studies were conducted on metabolites N-desmethyl, carboxylic acid and sulfonamide:

Acute oral toxicity N-desmethyl*	III	Acceptable	MRID 47070120
Acute oral toxicity carboxylic acid*	III	Acceptable	MRID 47070121
Acute oral toxicity sulfonamide*	III	Acceptable	MRID 47070210
Acute dermal toxicity sulfonamide**	III	Acceptable	MRID 47070211
Primary eye irritation sulfonamide**	III	Acceptable	MRID 47070206
Primary skin irritation sulfonamide**	IV	Acceptable	MRID 47070207
Dermal sensitization sulfonamide (mouse)**	Neg.	Supplemental	MRID 47070209

*UK conducted the primary review.
** UK did not review.

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for the proposed product as obtained from the Label Review System:

PRODUCT ID #: 000264-01060

PRODUCT NAME: Thiencarbazone-methyl Technical

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Harmful if absorbed through skin. Harmful if swallowed. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

First Aid:

If on skin: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

If swallowed: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Acute oral toxicity

Report:	**KIIA 5.2.1/02, Schüngel M.; 2006**
Title:	BYH 18636, Acute toxicity in the rat after oral administration
Citation:	Schugel, M. (2006) BYH 18636: Acute Toxicity in the Rat after Oral Administration. Project Number: AT03457, TXGSP054, T5077100. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 26 p. November 14, 2006. MRID No. 47070205
Report No & Document No	AT03457 M-286151-01-2
Guidelines:	OECD 423 (2001); EEC Directive 67/548 Annex V – Method B.1.tris (2004); EPA Health Effects test Guidelines (OPPTS 870.1100) (1998)
GLP	Yes (certified laboratory)

Executive Summary: Based on the specification required for production of the technical BYH 18636, a new acute oral rat study was required. In a stepwise procedure, two groups of three fasted, young adult female Wistar rats (HsdCpb:Wu) were given successively a single oral dose of BYH 18636 (batch number GELL 420-151-1, 94.6% purity) in 2% Cremophor EL of 2000 mg/kg bw and were observed for 14 days.

The dose of 2000 mg/kg bw was tolerated by both groups without mortalities, clinical signs, effects on weight gain or gross pathological findings.

The oral LD_{50} of BYH 18636 was > 2000 mg /kg bw and is classified as EPA toxicity Category III.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: BYH 18636
Description: White powder
Lot/Batch: GELL 420-151-1
Purity: 94.6%
CAS: 317815-83-1
Stability of test compound: Stable at 1 and 200 mg/ml at room temperature for 4 hours

2. Vehicle and /or positive control: 2% Cremophor EL in tap water

3. Test animals:

Species:	Rat
Strain:	HsdCpb:Wu
Age:	10 to 12 weeks approximately
Weight at dosing:	196 to 212 g
Source:	Harlan/Winkelmann GmbH, 33178 Borchen, Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were group caged conventionally in polycarbonate cages on low dust wood granulate bedding
Environmental conditions –	
Temperature:	22±2°C
Humidity:	55±5%
Air changes:	Approximately 10 changes per hour
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: July 19 to August 09, 2006

2. Animal assignment and treatment

The substance was tested using a stepwise procedure, each step using three female rats. The animals were assigned to their groups by randomization. The random list was based on evenly distributed chance numbers by a sofware application. Following an overnight fast (16 to 24 hours), each group received a single dose of 2000 mg/kg of BYH 18636 (94.6% purity) by gavage. The test substance was administered in tap water with 2% Cremophor EL at a volume of 10 ml/kg bw. Clinical signs and mortality rates were determined several times on the day of administration and subsequently at least once daily for an observation period of at least 14 days. Body weights were recorded on days 1, 8 and 15. On day 15, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Table IIA 5.2.1-2 Doses, mortality / animals treated

Dose (mg/kg bw)	Females
2000 (1st)	0/3
2000 (2nd)	0/3

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. MORTALITY

Details are provided in table IIA 5.2.1-2. No mortalities occurred at 2000 mg/kg bw, the only dose tested.

B. CLINICAL OBSERVATIONS

No clinical signs were observed.

C. BODY WEIGHT

There was no toxicological effect on body weight or body weight gain.

D. NECROPSY

No abnormalities were observed at gross necropsy.

III. CONCLUSION

The oral LD_{50} of BYH 18636 was > 2000 mg/kg bw.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's Comments	Reliability rating: Totally reliable The study (T 5077100) is fully compliant with OECD 423 (2001) No treatment-related findings were apparent in this study following the administration of a single gavage (limit) dose of 2000 mg/kg bw.
Conclusions	The acute oral LD50 of thiencarbazone-methyl in female rats was found to be >2000 mg/kg bw under the conditions of this study. Thiencarbazone-methyl (94.6% purity) is therefore not classified for acute oral toxicity according to current EC criteria. EPA: For Toxicity Category/Classification EPA Toxicity Category III – LD_{50} > 2000 mg/kg - would be assigned.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Acute oral toxicity

Report:	**KIIA 5.2.1/01, Schüngel M.; 2004**
Title:	BYH 18636, Acute toxicity in the rat after oral administration
Citation:	Schungel, M. (2004) BYH 18636: Acute Toxicity in the Rat After Oral Administration. Project Number: AT01452, TXGSX006, T/5074266. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 28 p. September 15, 2004. MRID No. 47070119
Report No & Document No	AT01452 M-088833-01-2
Guidelines:	OECD 423 (2001); EEC Directive 67/548 Annex V – Method B.1.tris (2004); EPA Health Effects test Guidelines (OPPTS 870.1100) (1998)
GLP	Yes (certified laboratory)

Executive Summary: In an acute oral toxicity study using a stepwise procedure, two groups of three fasted, young adult female Wistar rats (HsdCpb:Wu) were given successively a single oral dose of BYH 18636 (batch number MIX-batch 702-73-06-0001, 96.2% purity) in 2% Cremophor EL of 2000 mg/kg bw and were observed for 14 days.

The dose of 2000 mg/kg bw was tolerated by both groups without mortalities, clinical signs, effects on weight gain or gross pathological findings.

The oral LD_{50} of BYH 18636 was > 2000 mg /kg bw and is classified as EPA toxicity Category III.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: BYH 18636
Description: White powder
Lot/Batch: MIX-batch 702-73-06-0001
Purity: 96.2%
CAS: 317815-83-1
Stability of test compound: Stable at 1 and 200 mg/ml at room temperature for 4 hours

2. Vehicle and /or positive control: 2% Cremophor EL in demineralized water

3. Test animals:

Species:	Rat
Strain:	HsdCpb:Wu
Age:	10 to 14 weeks approximately
Weight at dosing:	167 to 183 g
Source:	Harlan/Winkelmann GmbH, 33178 Borchen, Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15 maus/Ratte Haltung, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were group caged conventionally in polycarbonate cages on low dust wood granulate bedding
Environmental conditions –	
Temperature:	22±2°C
Humidity:	55±5%
Air changes:	Approximately 10 changes per hour
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: 28 April to 18 May, 2004

2. Animal assignment and treatment

The substance was tested using a stepwise procedure, each step using three female rats. The animals were assigned to their groups by randomization. The random list was based on evenly distributed chance numbers by a sofware application. Following an overnight fast (16 to 24 hours), each group received a single dose of 2000 mg/kg of BYH 18636 (96.2% purity) by gavage. The test substance was administered in demineralized water with 2% Cremophor EL at a volume of 10 ml/kg bw. Clinical signs and mortality rates were determined several times on the day of administration and subsequently at least once daily for an observation period of at least 14 days. Body weights were recorded on days 1, 8 and 15. On day 15, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Table IIA 5.2.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Females
2000 (1st)	0/3
2000 (2nd)	0/3

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. MORTALITY

Details are provided in table IIA 5.2.1-1. No mortalities occurred at 2000 mg/kg bw, the only dose tested.

B. CLINICAL OBSERVATIONS

No clinical signs were observed.

C. BODY WEIGHT

There was no toxicological effect on body weight or body weight gain.

D. NECROPSY

No abnormalities were observed at gross necropsy.

III. CONCLUSION

The oral LD_{50} of BYH 18636 was > 2000 mg/kg bw.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's Comments	Reliability rating: Totally reliable The study (T 5074266) is fully compliant with OECD 423 (2001) No treatment-related findings were apparent in this study following the administration of a single gavage (limit) dose of 2000 mg/kg bw.
Conclusions	The acute oral LD50 of thiencarbazone-methyl in female rats was found to be >2000 mg/kg bw under the conditions of this study. Thiencarbazone-methyl (96.2% purity) is therefore not classified for acute oral toxicity according to current EC criteria. EPA: For Toxicity Category/Classification EPA Toxicity Category III – LD_{50} > 2000 mg/kg - would be assigned.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Acute dermal toxicity

Report:	**KIIA 5.2.2/01, Schüngel M.; 2004**
Title:	BYH 18636, Acute toxicity in the rat after dermal application
Citation:	Schungel, M. (2004) BYH 18636: Acute Toxicity in the Rat After Dermal Application. Project Number: TXGSX007, AT01445, T/0074270. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 28 p. September 13, 2004. MRID No. 47070122
Report No & Document No	AT 01445 M-088222-01-2
Guidelines:	OECD 402 (1987); EEC Directive 67/548 Annex V – Method B.3. (1992); EPA Health Effects Test Guidelines (OPPTS 870.1200; 1998)
GLP	Yes (certified laboratory)

Executive Summary: In an acute dermal toxicity study, groups of young adult Wistar rats, 5/sex were exposed by the dermal route to BYH 18636 (batch number MIX-batch 702-73-06-0001, 96.2% purity). The test material was applied as received for 24 hours to 10% of each animal's body surface at a dose of 2000 mg/kg. Animals were observed for the following 14 days.

The dermal LD_{50} for the males was > 2000 mg/kg bw, for the females was > 2000 mg/kg bw, for the combined sexes was > 2000 mg/kg bw.

BYH 18636 was regarded as of very low toxicity after dermal application. The only clinical sign observed was a partial reddening of the skin in one female from day 5 to day 7. Body weight and body weight gain of male rats were not affected by treatment. A decrease in body weight was observed on day 8 of the study in females. The females had recovered at the end of the study.

BYH 18636 is classified as EPA Toxicity Category III.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	BYH 18636
Description:	White powder
Lot/Batch:	MIX-batch 702-73-06-0001
Purity:	96.2%
CAS:	317815-83-1
Stability of test compound:	Technical material specified for the duration of the study

2. Vehicle and /or positive control: test material dosed as received moistened with water

3. Test animals:

Species:	Rat
Strain:	HsdCpb:Wu
Age:	9 to 13 weeks approximately
Weight at dosing:	237 to 263 g for the males – 219 to 225 g for the females
Source:	Harlan/Winkelmann GmbH, 33178 Borchen, Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were caged individually in polycarbonate cages on low dust wood granulate bedding
Environmental conditions –	
Temperature:	22±2°C
Humidity:	55±5%
Air changes:	Approximately 10 changes per hour
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: 29 April to 13 May, 2004

2. Animal assignment and treatment

Animals were assigned by randomization to the test groups listed in Table IIA 5.2.2.-1. The random list was based on evenly distributed chance numbers especially generated for the study by a software application. On the day prior to dosing, the fur was clipped from the dorsal area of the trunk of each animal (approximately 10% of the body surface area). The test substance was administered as a single occluded dermal application and was applied moistened with distilled water. After an exposure period of 24 hours, the occlusion was removed and residual test material was removed with tepid water using soap and gently patting the area dry. Animals were observed for clinical signs and mortality several times on the day of dosing and subsequently at least once daily for an observation period of at least 14 days. Individual body weights were recorded on days 1, 8 and 15. On day 15, all animals were sacrificed by carbon dioxide and were necropsied and examined for gross pathological changes.

Table IIA 5.2.2.-1: Doses, mortality / animals treated

Dose (mg/kg bw)	Males	Females	Combined
2000	0/5	0/5	0/10

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. MORTALITY

Details are provided in table IIA 5.2.2.-1. No mortalities occurred at 2000 mg/kg bw, the only dose level tested.

B. CLINICAL OBSERVATIONS

The only clinical sign observed was a partial reddening of the skin in one female from day 5 to day 7.

C. BODY WEIGHT

Body weight and body weight gain of male rats were not affected by treatment. A decrease in body weight was observed on day 8 for the females. The females had recovered at the end of the study.

D. NECROPSY

The necropsies performed at the end of the study revealed no particular findings.

III. CONCLUSION

The dermal LD_{50} of BYH 18636 was higher than 2000 mg/kg bw in both sexes.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's Comments	Reliability rating: Totally reliable The study (T 0074270)is fully compliant with OECD 402 (1987) Marginal weight loss was seen in females during Week 1; weight gain was seen in all animals during Week 2 however two females had not regained their initial weight by termination. No further treatment-related findings were apparent following a single dermal application at the limit dose.
Conclusions	The acute dermal LD50 of thiencarbazone-methyl in the rat was found to be >2000 mg/kg bw under the conditions of this study. Thiencarbazone-methyl is therefore not classified for acute dermal toxicity according to current EC criteria. EPA: For Toxicity Category/Classification EPA Toxicity Category III – LD_{50} > 2000 mg/kg - would be assigned.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Acute inhalation toxicity

Report:	**KIIA 5.2.3/01, Pauluhn J.; 2004**
Title:	BYH 18636, Acute inhalation toxicity in rats
Citation:	Pauluhn, J. (2004) BYH 18636: Acute Inhalation Toxicity in Rats. Project Number: TXGSX008, AT01473, T2073309. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 84 p. September 20, 2004. MRID No. 47070123
Report No & Document No	AT01473 M-089443-01-2
Guidelines:	OECD 403 (1981); EEC Directive 92/69 Annex V – Method B.2. (1992); EPA Health Effects Test Guidelines (OPPTS 870.1300; 1998); Japan MAFF, Notification N° 12 Nousan-8147 (2000)
GLP	Yes (certified laboratory)

Executive Summary: In an acute inhalation study, groups of young adult Wistar rats (5/sex) were exposed by the inhalation route to BYH 18636 (batch number MIX-batch 702-73-06-0001, 96.2% purity) in air for 4 hours (nose only) at a concentration of 1060, 2018 and 5158 mg/m^3, respectively. A concurrent control group was exposed to an atmosphere using similar exposure conditions (15 L/min; conditioned dry air). Animals were observed for the following 14 days.

The inhalation LC_{50} for the males was > 2018 mg/m^3, for the females was > 2018 mg/m^3, for the combined sexes was > 2018 mg/m^3.

BYH 18636 (solid aerosol) proved to be non-toxic via the inhalation route to rats. No mortality or treatment-related clinical signs occurred up to the maximum technically attainable concentration. No changes in the reflex behaviour were observed. The rectal temperature was not affected by the treatment. No treatment-related significant effects were noted on body weight evolution. At necropsy no treatment-related findings were reported.

BYH 18636 is classified as EPA Toxicity Category IV.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	BYH 18636
Description:	White powder
Lot/Batch:	MIX-batch 702-73-06-0001
Purity:	96.2%
CAS:	317815-83-1

Stability of test compound: certified for the duration of the study

2. Vehicle and /or positive control: the test substance was aerosolized as dry powder

3. Test animals:

Species:	Rat
Strain:	HsdCpb:Wu
Age:	2 months approximately
Weight at dosing:	174 to 234 g for the males and 161 to 194 g for the females
Source:	Harlan/Winkelmann GmbH, 33178 Borchen, Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883 = NAFAG 9441 pellets maintenance diet for rats and mice, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were individually caged in conventional Makrolon® Type III_H cages.
Environmental conditions –	
Temperature:	22±2°C
Humidity:	50±10%
Air changes:	Approximately 10 changes per hour
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: 11 May to 09 June, 2004

2. Animal assignment and treatment

Animals were assigned to the test groups listed in Table IIA 5.2.3-1. The random list was based on evenly distributed chance numbers especially generated for the study by a software application. Animals were exposed to the aerosolized test substance in Plexiglas exposure tubes applying a directed-flow nose-only exposure principle. Animals were examined carefully several times on the day of exposure and at least once daily thereafter for 2 weeks. The following reflexes were tested: visual placing response, grip strength on wire mesh, abdominal muscle tone, corneal and pupillary reflexes, pinnal reflex, righting reflex, tail-pinch response, startle reflex with respect to behavioural changes stimulated by sounds (finger snapping) and touch (back). The rectal temperatures were measured shortly after cessation of exposure. Individual body weights were recorded before exposure and on days 3, 7 and 14. On day 15, all animals were sacrificed, necropsied and examined for gross pathological changes.

Table IIA 5.2.3-1 Doses, mortality / animals treated

Analytical concentration (mg/m^3)	Males	Females	Combined
0	0/5	0/5	0/10
1060	0/5	0/5	0/10
2018	0/5	0/5	0/10
5158	0/5	0/5	0/10

3. Generation of the test atmosphere / chamber description

Directed-flow nose-only inhalation chambers (TSE, 61348 Bad Homburg) were used. Two methods for dust generation were used: a Wright-Dust-Feeding system for intermediate concentrations and an Exactomat for high concentrations. The test substance concentration was determined by gravimetric analysis. Chamber samples were collected after the equilibrium concentration had been attained in hourly intervals. Two samples during each exposure were also taken for the analysis of the particle-size distribution using a Berner-type Aeras low-pressure critical orifice cascade impactor.

Gravimetric concentration (mg/m^3)	1060	2017.5	5157.5
Mass median aerodynamic diameter (□m)	6.28	2.35	17.56
Geometric standard deviation	3.04	1.88	2.73
Aerosol Mass < 3 □m (%)	25.5	65.2	4.1

The limit concentration of 5000 mg/m^3 was attained, however, at the expense of larger particles (no cyclone used). At 5158 mg/m^3, the Mass Median Aerodynamic Diameter was 17.56 μm and only 4.1% of particles had an aerosol mass < 3 μm. In order to achieve a particle size < 4 □m the test was repeated at 2000 mg/m^3 using the micronized test article and a cyclone. At 2017.5 mg/m3, the Mass Median Aerodynamic Diameter was 2.35 μm and 65.2% of particles had an aerosol mass < 3 μm. The study is nevertheless acceptable.

4. Statistics

A one-way ANOVA (vide infra) was used to analyze body weight gain data and rectal temperature measurements.

II. RESULTS AND DISCUSSION

A. MORTALITY

No mortality occurred up to 2018 mg/m^3, the maximum technically achievable concentration.

The 4 hour inhalation LC_{50} for the males was > 2018 mg/m^3, for the females was > 2018 mg/m^3, for the combined sexes was > 2018 mg/m^3.

B. CLINICAL OBSERVATIONS

All rats tolerated the exposure without specific signs. A battery of reflex measurements was made on the first post-exposure day. In comparison to the rats of the control group, none of the rats of the treated groups exhibited changes in the reflex behavior. The rectal temperature was not affected by treatment.

C. BODY WEIGHT

Comparisons between the control and the exposure groups revealed no toxicologically significant changes in body weight in both sexes.

D. NECROPSY

Macroscopic changes causally related to the exposure of the test article were not observed.

III. CONCLUSION

The acute inhalation LC_{50} of BYH 18636 for the combined sexes was in excess of 2018 mg/m^3.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's Comments	Reliability rating: Totally reliable The study (T2073309) is fully compliant with OECD 403 (1981). The absence of treatment-related findings at the higher concentration of 5158 mg/m^3 (5.158 mg/l) is reassuring, however the large particle size (MMAD 17.56 ±2.73 µm) at this concentration is noted. As the large majority of particles at this concentration were not of respirable size, this concentration (stated to be the maximum achievable) is not considered to be suitable for the derivation of the LC50 value.
Conclusions	The acute inhalation LC50 of thiencarbazone-methyl in the rat was therefore found to be >2018 mg/m^3 (2.018 mg/l; MMAD 2.35 ±1.88 µm) under the conditions of this study. However the absence of treatment-related findings at any concentration indicates that thiencarbazone-methyl should not be classified for acute inhalation toxicity according to current EC criteria: further testing is therefore not required. The absence of an effect on rectal temperature in this study indicates that thiencarbazone-methyl is not a significant respiratory irritant. EPA: For Toxicity Category/Classification EPA Toxicity Category IV would be assigned.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Primary eye irritation

Report:	**KIIA 5.2.5/01, Schüngel M.; 2005**
Title:	BYH 18636, Acute eye irritation on rabbits
Citation:	Schungel, M. (2006) BYH 18636: Acute Eye Irritation on Rabbits. Project Number: TXGSP006, AT02437, T/4075381. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 22 p. September 27, 2005. MRID No. 47070124.
Report No & Document No	AT02437 M-259012-01-2
Guidelines:	OECD 405 (2002); EEC Directive 2004/73/EC Annex V – Method B.4. (2004); EPA Health Effects Test Guideline (OPPTS 870.2400; 1998)
GLP	Yes (certified laboratory)

Executive summary: In a primary eye irritation study, 0.1 g of pulverized test substance (MIX-batch 702-73-06-0001, 96.0% purity) was placed into the conjunctival sac of one eye of a rabbit after having gently pulled the lower lid away from the eyeball. The other eye, which remained untreated, served as control. Since severe irritation was not observed one hour after treatment, two further rabbits were treated as described. Eye irritation was scored and recorded at 1, 24, 48 and 72 hours after application. As no irritation indices were observed after 72 hours, the study was finished.

The degree of ocular lesions was recorded as specified by Draize and any serious lesion or toxic effects other than ocular lesions were also recorded. Body weight of each animal was recorded at the beginning of the study.

Positive scores for redness of the conjunctivae were observed in 3/3 eyes at the one hour observation. No positive scores were noted at 24 hours. All eyes were free of irritation by 48 hours.

BYH 18636 is classified as EPA Toxicity Category IV.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	BYH 18636
Description:	White powder
Lot/Batch:	MIX-batch 702-73-06-0001
Purity:	96.0%

Stability of test compound: Technical material specified for the duration of the study

2. Vehicle and /or positive control: test material dosed as received

3. Test animals:

Species:	Rabbit
Strain:	Crl:KBL(NZW)BR
Age:	Young adult animals
Weight at dosing:	2.6 to 3.2 kg
Source:	Charles River, 88353 Kißlegg, Germany
Acclimation period:	At least 5 days
Diet:	Ssniff K-Z 4mm (Ssniff Spezialdiäten GmbH, 59494 Soest, Germany), approximately 100 g per animal per day
Water:	Tap water, *ad libitum*
Housing:	Animals were caged individually in cage units Metall/Noryl by EBECO
Environmental conditions –	
Temperature:	20±3°C
Humidity:	50±25%
Air changes:	not mentioned
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: June 21 to 24, 2005

2. Animal assignment and treatment

The testing strategy comprised a stepwise approach including the evaluation of existing data, the performance of a SAR evaluation for eye and skin corrosion/irritation, measurement of pH value, the evaluation of data on systemic toxicity via the dermal route, the performance of a validated *in vitro* test for skin corrosion (Human 3D Epidermal Skin Model) and *in vivo* testing for skin irritation/corrosion in rabbits before *in vivo* testing for eye irritation/corrosion in rabbits.

On the day before dosing, both eyes of each animal were examined including fluorescein examination. Only animals with healthy intact eyes were used. 0.1 g of pulverized test substance was placed into the conjunctival sac of one eye of the first animal after having gently pulled the lower lid away from the eyeball. The lids were gently held together for about one second in order. to prevent loss of the test substance. The other eye, which remained untreated, served as control. The eye was not rinsed for at least 24 hours following instillation. One hour after treatment a severe irritation was not observed, so two further rabbits were treated as described. The eye irritation was scored and recorded at 1, 24, 48 and 72 hours after application. If no irritation was observed after 72 hours, the study was

72 hours after application. If no irritation was observed after 72 hours, the study was finished. If eye irritation was observed, animals were monitored usually on days 7, 14 and 21 after application until the changes had completely subsided, however for not more than 21 days after application.

The degree of ocular lesions was recorded as specified by Draize and any serious lesion or toxic effects other than ocular lesions were also recorded. Body weight of each animal was recorded at the beginning of the study.

II. RESULTS

A. FINDINGS

Positive scores for redness of the conjunctivae were observed in 3/3 eyes at the one hour observation. No positive scores were noted at 24 hours. All eyes were free of irritation by 48 hours.

Table IIA 5.2.5-1: Eye irritation scores according to the Draize scheme

	Cornea			Iris			Conjunctiva-redness			Conjunctiva-chemosis		
Animal number Time of observation	1	2	3	1	2	3	1	2	3	1	2	3
1 hour	0	0	0	0	0	0	2	2	3	0	0	0
24 hours	0	0	0	0	0	0	1	1	1	0	0	0
48 hours	0	0	0	0	0	0	0	0	0	0	0	0
72 hours	0	0	0	0	0	0	0	0	0	0	0	0
Mean scores 24-72 hours	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.3	0.3	0.0	0.0	0.0

Conjunctivae: Redness (refers to palpebral and bulbar conjunctivae; excluding cornea and iris)
Normal: 0 – Some blood vessels hyperaemic (injected): 1 – Diffuse, crimson colour; individual vessels not easily discernible: 2.
Chemosis: Swelling (refers to lids and/or nictating membranes)
Normal: 0 – Some swelling above normal: 1 – Obvious swelling, with partial eversion of lids: 2- Swelling, with lids about half closed: 3 – Swelling, with lids more than half closed

II. CONCLUSION

Based on the reversal of ocular irritation by 24 hours, BYH 18636 is classified as EPA Toxicity Category IV.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's Comments	Reliability rating: Totally reliable The study (T4075381) is fully compliant with OECD 405 (2002) Test animals were females. Signs of ocular irritation were limited to conjunctival erythema (up to Grade 3 according to the Draize scale); reactions declined in severity and were fully reversible within 48 hours. In order for classification as irritant the mean score for conjunctival redness needs to be $\geq$ 2.5 (mean score 24-72 hours individual animals).
Conclusions	The test material was found to be a mild eye irritant under the conditions of this study. The mean scores for ocular irritation are not sufficient to trigger classification of the test material as an eye irritant according to current EC criteria. EPA: Since there are no 'positive effects' at 24 hours, EPA Toxicity Category IV would be assigned.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Primary dermal irritation

Report:	**KIIA 5.2.4/01, Schüngel M.; 2004**
Title:	BYH 18636, Acute skin irritation/corrosion on rabbits
Citation:	Schungel, M. (2004) Acute Skin Irritation/Corrosion on Rabbits: BTH 18636. Project Number: T/3073788, AT01648, M/129093/01/2. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 21 p. December 1, 2004. MRID No. 47070203
Report No & Document No	AT01648 M-129093-01-2
Guidelines:	OECD 404 (2002); EEC Directive 2004/73/EC Annex V – Method B.4. (2004); EPA Health Effects Test Guideline (OPPTS 870.2500; 1998)
GLP	Yes (certified laboratory)

Executive summary: In a primary dermal irritation study, 3 young adult New Zealand female rabbits were exposed via the dermal route to 0.5 g of pulverized test substance (MIX-batch 702-73-06-0001, 96.3% purity) per animal. In the first step only one animal was used and three patches were applied successively to this animal. The first patch was removed after three minutes. As no serious skin reactions were observed, the second patch was removed after one hour and then the third patch applied and removed after four hours. The test was completed using two additional animals exposed for four hours. The test substance was applied as a powder moistened with water to the skin of the animal under a gauze patch. The animals were observed for 72 hours.

No erythema, eschar or œdema were observed at any time point. In this study, BYH 18636 was not a dermal irritant.

BYH 18636 is classified as EPA Toxicity Category IV.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: BYH 18636
Description: White powder
Lot/Batch: MIX-batch 702-73-06-0001
Purity: 96.3%
CAS: 317815-83-1
Stability of test compound: Technical material specified for the duration of the study

2. Vehicle and /or positive control: test material dosed as received moistened with water.

3. Test animals:

Species:	Rabbit
Strain:	Crl:KBL(NZW)BR
Age:	Young adult animals
Weight at dosing:	3.2 to 3.6 kg
Source:	Charles River, 88353 Kißlegg, Germany
Acclimation period:	At least 5 days
Diet:	Ssniff K-Z 4mm (Ssniff Spezialdiäten GmbH, 59494 Soest, Germany), approximately 100 g per animal per day
Water:	Tap water, *ad libitum*
Housing:	Animals were caged individually in cage units Metall/Noryl by EBECO
Environmental conditions –	
Temperature:	20±3°C
Humidity:	55±20%
Air changes:	not mentioned
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: October 26 to 29, 2004

2. Animal assignment and treatment

On the day prior to dosing, the fur was clipped on the right and left side from the dorsal-lateral area of the trunk of each rabbit. Care was taken to avoid abrading the skin. 0.5 g of the pulverized test substance moistened with water was applied to the skin of the animals under a gauze patch. The treated area was approximately 2.5 cm by 2.5 cm in size. The patch was placed on the dorso-lateral areas of the trunk of each rabbit and was held in place with non-irritating tape for the duration of the exposure period. After the exposure period the dressing and the patch were removed and the exposed skin area was carefully washed with water without altering the existing response, or the integrity of the epidermis. The contralateral skin area not treated with the test substance served as control.

In the first step only one animal was used and three patches were applied successively to this animal. The first patch was removed after three minutes. As no serious skin reactions were observed, the second patch was removed after one hour and then the third patch applied and removed after four hours. The test was completed using two additional animals exposed for four hours. The responses were graded one hour later.

The dermal irritation was scored at 1, 24, 48 and 72 hours after patch removal. If no irritation indices were observed after 72 hours, the study was finished. If dermal irritation was observed, animals were monitored usually on days 7 and 14 after patch removal. The degree of erythema/eschar formation and oedema formation was recorded as specified by Draize and

any serious lesion or toxic effects other than dermal irritation were also recorded. The body weight of each animal was recorded at the beginning of the study

II. RESULTS AND DISCUSSION

A. FINDINGS

No erythema, eschar or oedema was observed at any time point.

Table IIA. 5.2.4-1: Individual skin irritation scores according to the Draize scheme on the first animal

Observation (immediately after patch removal)	Duration of exposure	
	3 minutes	1 hour
Erythema (redness) And eschar formation	0	0
Oedema formation	0	0

Table IIA. 5.2.4-2: Individual and mean skin irritation scores after 4 hour exposure according the the Draize scheme

	Erythema and eschar			Oedema		
Animal number (body weight in kg)	1 (3.4)	2 (3.6)	3 (3.2)	1 (3.4)	2 (3.6)	3 (3.2)
1 hour	0	0	0	0	0	0
24 hours	0	0	0	0	0	0
48 hours	0	0	0	0	0	0
72 hours	0	0	0	0	0	0
Mean score 24-72 hours	0.0			0.0		
No positive response: mean scores < 2 = - Positive response : mean scores ≥ 2 = +						

III. CONCLUSIONS

BYH 18636 was a non-irritant to the rabbit skin.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's Comments	Reliability rating: Totally reliable The study (T3073788) is fully compliant with OECD 404 (2002) Test animals were females. No dermal reactions were observed in any animal at any time point.
Conclusions	No evidence of skin irritation was seen under the conditions of this study. Thiencarbazone-methyl is therefore not classified as a skin irritant according to current EC criteria. EPA: For Toxicity Category/Classification EPA Toxicity Category IV would be assigned.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Skin sensitization

Report:	**KIIA 5.2.6/01, Vohr H.-W.; 2004**
Title:	BYH 18636, Study for the skin sensitization effect in guinea pigs (Guinea pig maximization test according to Magnusson and Kligman)
Citation:	Vohr, H. (2004) BYH 18636: Study for the Skin Sensitization Effect in Guinea Pigs (Maximization Test According to Magnus and Kilgman). Project Number: AT01388, M/083284/01/2, T/5073096. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 31 p. August 9, 2004. MRID No. 47070204
Report No & Document No	AT01388 M-083284-01-2
Guidelines:	OECD 406 (1992); EEC Directive 96/54/EC Annex V – Method B.6. (1996); EPA Health Effects Test Guideline (OPPTS 870.2600; 2003)
GLP	Yes (certified laboratory)

Executive summary: In a dermal sensitisation study, BYH 18636 (MIX-batch 702-73-06-0001, 96.3% purity) in polyethylene glycol 400 was tested using young adult female SPF-bred guinea pigs of the strain Crl: HA. The treatment regime involved induction of sensitisation by intradermal injection of a suspension at 5% on day 1, induction of sensitisation by topical administration on day 8 and challenge by topical administration on day 22 of a suspension at 50%.

The challenge with the 50% BYH 18636 formulation led to no skin effects in the animals of the test substance group and the control group. Appropriate historical control data using alpha hexyl cinnamic aldehyde formulated in polyethylene glycol 400 demonstrated a positive response.

Based on the results of this study, BYH 18636 is classified as a non-sensitizer.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	BYH 18636
Description:	White powder
Lot/Batch:	MIX-batch 702-73-06-0001
Purity:	96.3%
CAS:	317815-83-1
Stability of test compound:	stable in vehicle at 1 and 50 % for at least 2 hours at room temperature

2. Vehicle and /or positive control: test material formulated in polyethylene glycol 400

3. Test animals:

Species:	Guinea pig
Strain:	Crl: HA
Age:	Young adult female animals
Weight at dosing:	296 to 384 g
Source:	Charles River, 88353 Kißlegg, Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3420 – maintenance Diet for Guinea pigs – (supplied by Provimi Kliba AG) *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were caged by two or three in type IV Makrolon® Cages

Environmental conditions –

Temperature:	22±3°C
Humidity:	55±15%
Air changes:	at least 10 times per hour
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: June 15 to July 09, 2004

2. Animal assignment and treatment

The treatment regime involved induction of sensitization by intradermal injection on day 1, induction of sensitization by topical administration on day 8 and challenge by topical administration on day 22. The doses for the induction and challenge treatments were selected on the basis of the results of the dose range-finding studies. Seven guinea pigs were used for those dose-range studies. The dorsal region and the flanks of the guinea pigs were shorn one day prior to the intradermal induction. Three injections were made on the left and the right side of the spinal column for each animal. Twenty animals were used for the test substance treated group and ten for the control group. All animals received at the first injection site complete Freund's adjuvant diluted with sterile physiological saline solution (1:1), at the second injection site 5% BYH 18636 formulated in polyethylene glycol 400 for the treated animals or vehicle alone for the control animals, and at the third injection site 5% BYH 18636 formulated at equal parts in polyethylene glycol 400 and complete Freund's adjuvant for treated animals or 1:1 mixture of polyethylene glycol 400 and complete Freund's adjuvant for control animals. The injection sites were visually assessed 2 and 7 days after the injection. The topical induction was performed one week after the intradermal induction. On the day prior to topical treatment, the test areas of the animals were shorn. Hypoallergenic patches were placed between and on the injection sites, covered with aluminum foil and held

securely in place using an ORABAND® self-adhesive tape. In the treated group, 0.5 ml of 50% BYH 18636 formulation was applied to the skin and in the control group, 0.5 ml of polyethylene glycol 400 was applied. At the end of the 48 hours exposure period, the remaining test item was removed with sterile physiological saline solution. The challenge was performed three weeks after the intradermal induction. The dorsal region and the right flank of the animals were shorn one day prior to the challenge. A 50% formulation of BYH 18636 was placed on the right flank of the treated and control animals and vehicle was also placed and covered with a patch on the right flank of all animals as control. At the end of the exposure period, the remaining test item was removed with physiological saline solution, and 21 hours later the skin of the animals was shorn in the zone of the challenge area. The skin reactions were assessed 48 and 72 hours after the start of the application.

II. RESULTS AND DISCUSSION

Appearance, behaviour and mean body weight of the treated group were not different from the control group. After the intradermal induction the animals in the control group and in the treated group showed strong effects up to encrustation at the injection sites of the first induction. The challenge with the 50% BYH 18636 formulation led to no skin effects in the animals of the BYH 18636 treated group and the control group. Appropriate historical control data using alpha hexyl cinnamic aldehyde formulated in polyethylene glycol 400 demonstrated a positive response.

III. CONCLUSION

BYH 18636 did not exhibit dermal sensitisation potential under the test conditions.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's Comments	Reliability rating: Totally reliable The study (T 4073040) is fully compliant with OECD 406 (1992) Dermal reactions following topical induction are not reported, however the concentration of the test material appears to be the highest achievable as a suspension in the vehicle. No dermal reactions were apparent following the challenge application. Although the Local Lymph Node Assay (LLNA) is PSD's preferred method for the assessment of skin sensitisation for reasons of animal welfare, the Maximisation method is scientifically valid and the result of this study are accepted.
Conclusions	No evidence of skin sensitisation was seen under the conditions of this study. The test material is therefore not classified as a skin sensitiser according to current EC criteria.

SUMMARY OF ACUTE TOXICITY, IRRITANCY AND SENSITISATION STUDIES BY REGULATORY AUTHORITY
Name of authority: Pesticides Safety Directorate, UK
All of the acute toxicity studies were conducted in 2004, except for a second acute oral rat study conducted in 2006 with material stated to be 'based on the specification required for production'. All studies were fully compliant with Good Laboratory Practice (GLP) and were conducted in accordance with the relevant prevailing OECD guideline. Studies were performed with thiencarbazone-methyl of 96.2-96.3% of purity; the additional study of acute oral toxicity was performed with material of 94.6% purity. Thiencarbazone-methyl was found to be of low acute toxicity to the rat by the oral, dermal and inhalation routes. No treatment-related findings were observed in the acute oral toxicity study at the limit dose level of 2000 mg/kg bw. Findings in the two acute oral toxicity studies using material of slightly different purity are comparable, indicating that the increased impurity levels (or additional impurities) present in the material of lower purity (and representative of the proposed specification) do not significantly influence acute oral toxicity. Treatment-related findings in the acute dermal toxicity were limited to minor bodyweights effects at the limit dose level of 2000 mg/kg bw. No treatment-related findings were observed at the highest concentration of 5158 mg/m^3 (5.158 mg/l) in the acute inhalation toxicity study, however the large particle size (MMAD 17.56 ±2.73 µm) at this concentration means that the majority of particles at this concentration are not of respirable size. The acute inhalation LC50 of thiencarbazone-methyl in the rat was found to be >2018 mg/m^3 (2.018 mg/l) under the conditions of this study. The absence of treatment-related findings at any concentration indicates that thiencarbazone-methyl should not be classified for acute inhalation toxicity according to current EC criteria. The absence of an effect on rectal temperature indicates that thiencarbazone-methyl is not a significant respiratory irritant. Thiencarbazone-methyl was not irritating to rabbit skin and caused moderate, reversible ocular irritation. No evidence of skin sensitisation (delayed contact hypersensitivity) was seen in a guinea pig Magnusson and Kligman maximisation test. Thiencarbazone-methyl is therefore not classified for acute toxicity or irritation according to current EC criteria.

Table IIA 5.2-1: Summary of acute toxicity data for BYH 18636

Type of study (Document N°)	**Species**	**Results**	**OECD Classification (proposed)**	**EPA Classification (proposed)**
Oral route M-088833-01-2	Rat	LD_{50} > 2 000 mg/kg,	Category 5 / Unclassified ($_{LD50}$ cut off ≥ 5000 mg/kg)	Category III (LD_{50} > 2000 mg/kg)
Oral route M-286151-01-2	Rat	LD_{50} > 2 000 mg/kg,	Category 5 / Unclassified ($_{LD50}$ cut off ≥ 5000 mg/kg)	Category III (LD_{50} > 2000 mg/kg)
Dermal route M-088222-01-2	Rat	LD_{50} > 2 000 mg/kg,	Category 5 / Unclassified	Category III
Inhalation M-089443-01-2	Rat	LC_{50} at 4 hours > 2018 mg/m^3	Category 5 / Unclassified	Category IV
Primary skin irritation M-129093-01-2	Rabbit	Non irritating	Category 5 / Unclassified	Category IV
Eye irritation M-129264-01-2	Rabbit	Slight to moderate redness and chemosis of the conjunctivae at one hour, reversed within 48 hours	Category 5 / Unclassified	Category IV
Skin sensitization M-083284-01-2	Guinea pig	Not sensitising	Category 5 / Unclassified	Negative

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Metabolite: BYH 18636-carboxylic acid

Acute oral toxicity

Report:	**KIIA 5.8/04, Schüngel M.; 2006**
Title:	BYH 18636-carboxylic acid (AE 1394083), Acute toxicity in the rat after oral administration
Citation:	Schungel, M. (2006) BYH 18636-carboxylic acid (AE 1394083): Acute Toxicity in the Rat After Oral Administration. Project Number: TXGSP028, AT02902, T/3076352. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 26 p. March 14, 2006. MRID No. 47070121
Report No & Document No	AT02902 M-269981-01-2
Guidelines:	OECD 423 (2001); EEC Directive 67/548 Annex V – Method B.1.tris (2004); EPA Health Effects test Guidelines (OPPTS 870.1100) (1998)
GLP	Yes (certified laboratory)

Executive Summary: In an acute oral toxicity study using a stepwise procedure, two groups of three fasted, young adult female Wistar rats (HsdCpb: Wu) were given successively a single oral dose of BYH 18636-carboxylic acid (batch GSE29091-9-1, 98.7% purity) in 2% Cremophor EL of 2000 mg/kg bw and were observed for 14 days.

The dose of 2000 mg/kg bw was tolerated by both groups without mortalities, clinical signs, effects on weight gain or gross pathological findings.

The oral LD_{50} of BYH 18636-carboxylic acid was > 2000 mg /kg and is classified as EPA Toxicity category III.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	BYH 18636-carboxylic acid
Description:	White solid
Lot/Batch:	GSE29091-9-1
Purity:	98.7% (December, 2005)
CAS:	No CAS entry yet
Stability of test compound:	Stable at 5 and 200 mg/ml at room temperature for at least 2 hours
2. Vehicle and /or positive control:	2% Cremophor EL in demineralized water
3. Test animals:	

Species:	Rat
Strain:	HsdCpb:Wu
Age:	10 to 12 weeks approximately
Weight at dosing:	164 to 176 g
Source:	Harlan/Winkelmann GmbH, 33178 Borchen, Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15 maus/Ratte Haltung, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were group caged conventionally in polycarbonate cages on low dust wood granulate bedding

Environmental conditions –

Temperature:	22±2°C
Humidity:	55±5%
Air changes:	Approximately 10 changes per hour
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: February 02 to 22, 2006 performed at Bayer HealthCare AG, Germany

2. Animal assignment and treatment

The substance was tested using a stepwise procedure, each step using three female rats. The animals were assigned to their groups by randomization based on evenly distributed chance numbers. Following an overnight fast (16 to 24 hours), each group received a single dose of 2000 mg/kg of BYH 18636-carboxylic acid (98.7% purity) by gavage. The test substance was administered in demineralized water with 2% Cremophor EL at a volume of 10 ml/kg bw. Clinical signs and mortality rates were determined several times on the day of administration and subsequently at least once daily for an observation period of at least 14 days. Body weights were recorded on days 1, 8 and 15. On day 15, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Table IIA 5.8-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Females
2000 (1st)	0/3
2000 (2nd)	0/3

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. MORTALITY

No mortalities occurred at 2000 mg/kg bw, the only dose tested.

B. CLINICAL OBSERVATIONS

No clinical signs were observed.

C. BODY WEIGHT

There was no toxicological effect on body weight or body weight gain.

D. NECROPSY

No abnormalities were observed at gross necropsy.

III. CONCLUSION

The oral LD_{50} of BYH 18636-carboxylic acid was > 2000 mg/kg .

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's comments	Reliability rating: Totally reliable The study (T3076352) is fully compliant with OECD guideline 423 (2001). No treatment-related findings were apparent in this study following a single (limit) dose of 2000 mg/kg bw.
Conclusions	The acute oral LD_{50} of thiencarbazone-methyl carboxylic acid in female rats was found to be >2000 mg/kg bw under the conditions of this study. The test material is not classified for acute oral toxicity according to current EC criteria. EPA: For Toxicity Category/Classification EPA Toxicity Category III – LD_{50} > 2000 mg/kg - would be assigned.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Metabolite: BYH 18636-sulfonamide

Acute oral toxicity

Report:	**KIIA 5.8/07, Schüngel M.; 2006**
Title:	BYH 18636-sulfonamide, Acute toxicity in the rat after oral administration
Citation:	Schungel, M. (2006) BYH 18636-Sulfonamide: Acute Toxicity in the Rat After Oral Administration. Project Number: AT03210, T/8076771, M/277277/01/2. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 26 p. MRID No. 47070210
Report No & Document No	AT03210 M-277277-01-2
Guidelines:	OECD 423 (2001); EEC Directive 67/548 Annex V – Method B.1.tris (2004); EPA Health Effects test Guidelines (OPPTS 870.1100) (1998)
GLP	Yes (certified laboratory)

Executive Summary: In an acute oral toxicity study using a stepwise procedure, two groups of three fasted, young adult female Wistar rats (HsdCpb: Wu) were given successively a single oral dose of BYH 18636-sulfonamide (batch CHZC007326, 99.0% purity) in 2% Cremophor EL of 2000 mg/kg bw and were observed for 14 days.

The dose of 2000 mg/kg bw was tolerated by both groups without mortalities, clinical signs, effects on weight gain or gross pathological findings.

The oral LD_{50} of BYH 18636-sulfonamide was > 2000 mg /kg bw and is classified as EPA Toxicity category III.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	BYH 18636-sulfonamide
Description:	light brown solid
Lot/Batch:	CHZC007326
Purity:	99.0% (March 2006)
CAS:	317815-81-9
Stability of test compound:	Stable at 5 and 200 mg/ml at room temperature for at least 2 hours
2. Vehicle and /or positive control:	2% Cremophor EL in demineralized water

3. Test animals:

Species:	Rat
Strain:	HsdCpb: Wu
Age:	10 to 12 weeks approximately
Weight at dosing:	160 to 175 g
Source:	Harlan/Winkelmann GmbH, 33178 Borchen, Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were group caged conventionally in polycarbonate cages on low dust wood granulate bedding

Environmental conditions –

Temperature:	22±2°C
Humidity:	55±5%
Air changes:	Approximately 10 changes per hour
Photoperiod :	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: April 26 to May 17, 2006 performed at Bayer HealthCare AG, Germany

2. Animal assignment and treatment

The substance was tested using a stepwise procedure, each step using three female rats. The animals were assigned to their groups by randomization based on evenly distributed chance numbers. Following an overnight fast (16 to 24 hours), each group received a single dose of 2000 mg/kg of BYH 18636-sulfonamide (99.0% purity) by gavage. The test substance was administered in demineralized water with 2% Cremophor EL at a volume of 10 ml/kg bw. Clinical signs and mortality rates were determined several times on the day of administration and subsequently at least once daily for an observation period of at least 14 days. Body weights were recorded on days 1, 8 and 15. On day 15, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Table IIA 5.8-5 Doses, mortality / animals treated

Dose (mg/kg bw)	Females
2000 (1st)	0/3
2000 (2nd)	0/3

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. MORTALITY

No mortalities occurred at 2000 mg/kg bw, the only dose tested.

B. CLINICAL OBSERVATIONS

No clinical signs were observed.

C. BODY WEIGHT

There was no toxicological effect on body weight or body weight gain.

D. NECROPSY

No abnormalities were observed at gross necropsy.

III. CONCLUSION

The oral LD_{50} of BYH 18636-sulfonamide was > 2000 mg/kg bw.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's comments	Reliability rating: Totally reliable The study (T8076771) is fully compliant with OECD 423 (2001) No treatment-related findings were seen following the administration of a single (limit) dose of 2000 mg/kg bw.
Conclusions	The acute oral LD50 of thiencarbazone-methyl-sulphonamide in female rats was found to be >2000 mg/kg bw under the conditions of this study. The test material is therefore not classified for acute oral toxicity according to current EC criteria. EPA: For Toxicity Category/Classification EPA Toxicity Category III – LD_{50} > 2000 mg/kg - would be assigned.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Metabolite: BYH 18636-N-desmethyl

Acute oral toxicity

Report:	**KIIA 5.8/12, Schüngel M.; 2007**
Title:	BYH 18636-N-desmethyl, Acute toxicity in the rat after oral administration
Citation:	Schungel, M. (2007) BYH 18636 N-desmethyl: Acute Toxicity in the Rat After Oral Administration. Project Number: TXGSP055, AT03550, T/1077241. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 29 p. July 18, 2006. MRID No. 47070120
Report No & Document No	AT03550 M-283442-01-2
Guidelines:	OECD 423 (2001); EEC Directive 67/548 Annex V – Method B.1.tris (2004); EPA Health Effects test Guidelines (OPPTS 870.1100) (1998)
GLP	Yes (certified laboratory)

Executive Summary: In an acute oral toxicity study using a stepwise procedure, two groups of three fasted, young adult female Wistar rats (HsdCpb: Wu) were given successively a single oral dose of BYH 18636-N-desmethyl (batch KATH 4779-3-12, 98.9% purity) in 2% Cremophor EL of 2000 mg/kg bw and were observed for 14 days.

The dose of 2000 mg/kg bw was tolerated by both groups without mortalities, clinical signs, effects on weight gain or gross pathological findings.

The ora LD_{50} of BYH 18636-N-desmethyl was > 2000 mg /kg bw and is classified as EPA Toxicity Category III.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	BYH 18636-N-desmethyl
Description:	Off-white solid
Lot/Batch:	KATH 4776-3-12
Purity:	98.9% (August 21, 2006)
CAS:	No CAS entry yet
Stability of test compound:	Stable at 5 and 200 mg/ml at room temperature for at least 2 hours
2. Vehicle and /or positive control:	2% Cremophor EL in demineralized water

3. Test animals:

Species:	Rat
Strain:	HsdCpb: Wu
Age:	10 to 12 weeks approximately
Weight at dosing:	167 to 182 g
Source:	Harlan/Winkelmann GmbH, 33178 Borchen, Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were group caged conventionally in polycarbonate cages on low dust wood granulate bedding

Environmental conditions –

Temperature:	22±2°C
Humidity:	55±5%
Air changes:	Approximately 10 changes per hour
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: September 27 to October 19, 2006 performed at Bayer HealthCare AG, Germany

2. Animal assignment and treatment

The substance was tested using a stepwise procedure, each step using three female rats. The animals were assigned to their groups by randomization based on evenly distributed chance numbers. Following an overnight fast (16 to 24 hours), each group received a single dose of 2000 mg/kg of BYH 18636-N-desmethyl (98.9% purity) by gavage. The test substance was administered in demineralized water with 2% Cremophor EL at a volume of 10 ml/kg bw. Clinical signs and mortality rates were determined several times on the day of administration and subsequently at least once daily for an observation period of at least 14 days. Body weights were recorded on days 1, 8 and 15. On day 15, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Table IIA 5.8-9 Doses, mortality / animals treated

Dose (mg/kg bw)	Females
2000 (1st)	0/3
2000 (2nd)	0/3

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. MORTALITY

No mortalities occurred at 2000 mg/kg bw, the only dose tested.

B. CLINICAL OBSERVATIONS

No clinical signs were observed.

C. BODY WEIGHT

There was no toxicological effect on body weight or body weight gain.

D. NECROPSY

No abnormalities were observed at gross necropsy.

III. CONCLUSION

The oral LD_{50} of BYH 18636-N-desmethyl was > 2000 mg/kg bw.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's comments	Reliability rating: Totally reliable The study (T1077241) is fully compliant with OECD 423 (2001) No treatment-related findings were observed following gavage with a single (limit) dose of 2000 mg/kg bw.
Conclusions	The acute oral LD50 of thiencarbazone-methyl desmethyl in female rats was found to be >2000 mg/kg bw under the conditions of this study. The test material is therefore not classified for acute oral toxicity according to current EC criteria. EPA: For Toxicity Category/Classification EPA Toxicity Category III – LD_{50} > 2000 mg/kg - would be assigned.

Reviewer: Rick J. Whiting **Date:** February 15, 2008
Risk Manager: Hope Johnson RM 25

STUDY TYPE: Acute Dermal Toxicity - Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: BYH 18636-sulfonamide (Purity: 99.0%; Batch No. CHZC007326; CAS No. 317815-81-9; light brown solid)

CITATION: Schungel, T. (2006) BYH 18636-Sulfonamide: Acute Toxicity in the Rat After Dermal Application. Project Number: AT03211, T 9076772, M-277279-01-2. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 27 p. July 18, 2006. MRID No. 47070211

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 4707070211), five male and five female Wistar rats (strain HsdCpb:Wu; age: 9-13 weeks, weight: 238-260 g males, 206-225 g females; source: Harlan/Winkelmann GmbH, 33178 Borchen, Germany) were dermally exposed to 2000 mg/kg body weight of BYH 18636-sulfonamide (Purity: 99.0%; Batch No. CHZC007326; CAS No. 317815-81-9; light brown solid). The test material was applied to a clipped area of approximately 10% of the body surface area. For each animal the test material was weighed and transferred to a wet gauze-layer of "Cutiplast® steril" coated with air-tight "Leukoflex®". The gauze strip was placed on the animal's back and secured in place using "Peha®-Haft" cohesive stretch tape and additionally covered with a "Lomir biomedical Inc rat jacket", which was connected with a safety pin to the stretch tape to prevent the animals from ingesting the test material. After 24 hours the dressings were removed and the area was rinsed with tepid water using soap and gently patting the area dry.

Observations for mortality and clinical signs of toxicity were made several times on the day of application (defined as day 1) and at least once daily thereafter for an observation period of at least 14 days. Body weights were recorded on days 1, 8 and 15. A gross necropsy examination was performed on all animals at scheduled euthanasia.

All animals survived the study. One male and one female had slight body weight loss during the first week but surpassed their initial body weight by the end of the study. The remaining animals all gained weight during the study. No clinical signs or gross abnormalities were noted.

Dermal LD_{50} Males > 2000 mg/kg bw
Dermal LD_{50} Females > 2000 mg/kg bw
Dermal LD_{50} Combined > 2000 mg/kg bw

BYH 18636-sulfonamide is classified as EPA Toxicity Category III based on the observed LD_{50} value in both sexes.

This acute dermal study is classified Acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10

Statistics: The dermal LD_{50} was calculated using the limit dose.

A. **Mortality:** as noted in table.

B. **Clinical observations:** No clinical signs were noted.

C. **Gross Necropsy:** No gross abnormalities were noted.

D. **Reviewer's Conclusions:** The reviewer agrees with the study author's LD_{50}. BYH 18636-sulfonamide is classified as EPA Toxicity Category III.

E. **Deficiencies:** None.

Reviewer: Rick J. Whiting
Risk Manager: Hope Johnson RM 25

Date: February 15, 2008

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: BYH 18636-sulfonamide (Purity: 99.0%; Batch No. CHZC007326; CAS No. 317815-81-9; light brown solid)

CITATION: Gmelin, C. (2006) BYH 18636-[Inert Ingredient]: Acute Eye Irritation on Rabbits. Project Number: AT03432, T 4076579, M-280712-01-2. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 22 p. November 9, 2006. MRID No. 47070206

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47070206), 0.1 g of pulverized BYH 18636-sulfonamide (Purity: 99.0%; Batch No. CHZC007326; CAS No. 317815-81-9; light brown solid) was placed into the conjunctival sac of one eye of one young adult female albino rabbits (strain Crl:KBL(NZW)BR; weight: 2.7 kg; source: Charles River, 88353 Kißlegg, Germany). The lids were gently held together for about one second in order to prevent loss of test compound. The other untreated eye served as control. The eye was not rinsed for at least 24 hours following instillation. If after one hour a severe irritation was not observed, two further rabbits were treated as described. All animals were observed for ocular irritation and lesions at 1, 24, 48 and 72 hours after instillation. Ocular irritation was evaluated by the method of Draize.

No corneal opacity or iritis was observed in any of the treated eyes. Conjunctival redness (score 2) was noted in one rabbit at 1 and 24 hours. All conjunctival irritation was resolved by 72 hours.

Based on the conjunctival redness observed at 24 hours, BYH 18636-sulfonamide was considered to be mildly irritating and classified as EPA Toxicity Category III.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested			
	Hours			
	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae:				
Redness*	1/3	1/3	0/3	0/3
Chemosis*	0/3	0/3	0/3	0/3

*Score of 2 or more required to be considered "positive."

A. Observations: No corneal opacity or iritis was observed in any of the treated eyes. Conjunctival redness (score 2) was noted in one rabbit at 1 and 24 hours. All conjunctival irritation was resolved by 72 hours.

B. Reviewer's Conclusions: The study author concludes (from page 18 of study) "According to classification criteria BYH 1836-sulfonamide is not irritating to eyes." The TRB reviewer disagrees with this statement. Based on EPA's Acute Toxicity Categories, BYH 18636-sulfonamide was classified as EPA Toxicity Category III based on the conjunctival irritation observed at 24 hours.

C. Deficiencies: None.

Reviewer: Rick J. Whiting
Risk Manager: Hope Johnson RM 25

Date: February 15, 2008

STUDY TYPE: Primary Dermal Irritation - Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: BYH 18636-sulfonamide (Purity: 99.0%; Batch No. CHZC007326; CAS No. 317815-81-9; light brown solid)

CITATION: Gmelin, C. (2006) BYH 18636-[Inert Ingredient]: Acute Skin Irritation/Corrosion on Rabbits. Project Number: AT03439, T 3076578, M-280713-01-2. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 22 p. November 9, 2006. MRID No. 47070207

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47070207), three young female adult rabbits (strain Crl:KBL(NZW)BR; weight: 2.7-2.9 kg; source: Charles River, 88353 Kißlegg, Germany) were dermally exposed to 0.5 g of BYH 18636-sulfonamide (Purity: 99.0%; Batch No. CHZC007326; CAS No. 317815-81-9; light brown solid) for 4 hours. The test material was moistened with water and applied to the skin of the test animal under a gauze patch. The treated skin area was approximately 2.5 cm by 2.5 cm in size. The patch was held in place with non-irritating tape for the duration of the exposure period. After the exposure period the dressing and patch were removed and the exposed skin area was washed with water. "Due to a possible irritant potential of the test substance, in the first step only one animal was used and three test patches were applied successively to this animal, as described above. The first patch was removed after three minutes. As no serious skin reactions were observed, the second patch was applied and removed after one hour. At his stage, the observations indicated that with respect to animal welfare the exposure cane be allowed to extend to four hours, therefore the third patch was applied and removed after four hours and the responses were graded one hour later. The test was completed using two additional animals, exposed for four hours." The animals were observed and dermal irritation was scored at 1, 24, 48, and 72 hours after pathc removal as specified by Draize.

No erythema, edema, or other signs of dermal irritation were noted.

In this study, BYH 18636-sulfonamide is non-irritating and is classified as EPA Toxicity Category IV for primary dermal irritation. The Primary Irritation Index (PII) = 0.0.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

INDIVIDUAL SKIN IRRITATION SCORES

ERYTHEMA/EDEMA

Animal No.	Sex	Hours After Patch Removal			
		1	24	48	72
1	F	0/0	0/0	0/0	0/0
2	F	0/0	0/0	0/0	0/0
3	F	0/0	0/0	0/0	0/0

A. Observations: No erythema, edema, or other signs of dermal irritation were noted.

B. Results: Primary Dermal Irritation Index (PDII) = 0.0

C. Reviewer's Conclusions: In agreement with the study author, BYH 18636-sulfonamide is nonirritating and is classified in EPA Toxicity Category IV.

D. Deficiencies: None.

EPA Reviewer: Eugenia McAndrew **Date:** February 15, 2008
EPA Risk Manager: Hope Johnson RM 25

STUDY TYPE: Dermal Sensitization (Mouse): OPPTS 870.2600; OECD 429

TEST MATERIAL (PURITY): BYH 18636-Sulfonamide (Batch Number CHZC007326; 99.0%; pH (2% in water) 4.9; light brown solid)

CITATION: Repetto-Larsay, M. (2007). Evaluation of potential dermal sensitization in the local lymph node assay in the mouse. Bayer CropScience, 355, rue Dostoievski, BP 153, 06903 Sophia Antipolis Cedex, France. Laboratory study number SA 06367. February 28, 2007. MRID 47070209 Unpublished.

SPONSOR: Bayer CropScience AG, Alfred Nobel Str. 50. 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47070209) with BYH 18636-Sulfonamide (Batch Number CHZC007326; 99.0%; pH (2% in water) 4.9; light brown solid), 20 young female mice (CBA/J; age: 8 weeks; wt. 18.9-23 g; source: Bayer CropScience, Monheim, Germany; 5 animals / group) were tested using the method of local lymph node assay (LLNA). Dimethylsulfoxide (DMSO) was selected as the vehicle to ensure compatability with the test substance and maximum wetting of the mouse ears. Three groups of five mice received the test substance at a concentration of 5, 10 or 25% in vehicle. One control group received the vehicle only.

The test substance and vehicle were applied on the external surfaces of each mouse ear (25µL/ear) for three consecutive days at a concentration of 5, 10 or 25%.

On test day 5 of the study, the mice received 20 µCi of ^{3}H-thymidine by tail vein injection and were sacrificed approximately 5 hours later. The draining auricular lymph nodes were removed. The lymph nodes from each group of five were pooled in a tube containing physiological saline and were disaggregated by crushing with a plastic piston. A cell suspension was obtained, free of connective tissue. On test day 6, the cell suspensions were added to scintillation pots containing 10 mL of scintillation fluid and assayed in a beta counter. The results were expressed as disintergrations per minute (DPM) per node. Stimulation indices (SI) were calculated according to the following formula: $SI = \frac{\text{DPM of treated group}}{\text{DPM of control group}}$
The criterion for a positive response would be statistically significant increases in cell proliferation in the test concentration groups compared to the vehicle control group and/or SIs greater than or equal to 3.0.

The site of application was examined for signs of local irritation. The animals were checked for mortality and clinical signs at least once a day during the study. Individual animal body weights were measured at the start and end of the test.

No mortality and no clinical signs were observed during the study. No cutaneous reactions were observed at the treated sites. The proliferation index values of the test substance were 1.6, 1.5 and 1.2 at treatment concentrations of 5, 10 and 25%, respectively.

Based on the results of this study, there is no indication that BYH 18636-Sulfonamide is a dermal sensitizer. However, due to the deviations, the study is classified as supplementary. While it does not satisfy the guideline requirement for an acceptable dermal sensitization study (OPPTS 870.2600, OECD 429) in the mouse, since the test material is a metabolite, TRB can accept it as supplementary data. This study may not be used to support registration of the test material.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS and METHODS

A. Vehicle and positive control - The vehicle for this study was Dimethylsulfoxide (DMSO). A positive control study was not run concurrently and no historical data were provided.

B. Treatment preparation and administration - Three groups of five mice received the test substance at a concentration of 5, 10 or 25% in vehicle. One control group received the vehicle only. The test substance and vehicle were applied on the external surfaces of each mouse ear (25µL/ear) for three consecutive days at a concentration of 5, 10 or 25%. On test day 5 of the study, the mice received 20 µCi of ^{3}H-thymidine by tail vein injection and were sacrificed approximately 5 hours later. The draining auricular lymph nodes were removed. The lymph nodes from each group of five were pooled in a tube containing physiological saline and ere disaggregated by crushing with a plastic piston. A cell suspension was obtained, free of connective tissue. On test day 6, the cell suspensions were added to scintillation pots containing 10 mL of scintillation fluid and assayed in a beta counter. The results were expressed as disintegrations per minute (DPM) per node.

II. RESULTS and DISCUSSION:

A. Disintegrations per Minute (DPM) / node and Stimulation Index (SI) -

Concentration %	Pooled Treatment Group DPM	DPM/Node [a]	Stimulation Index (SI)*
0 Vehicle control	4773	477.3	n/a [b]
5	7492	749.2	1.6
10	7051	705.1	1.5
25	5638	563.8	1.2

[a] DPM/Node = Pooled Treatment Group DPM divided by 10 (the total number of lymph nodes per group)
[b] n/a = not applicable.
*SI = Group DPM ÷ Vehicle Control DPM

B. Stimulation Index -

Sample Description Test or Control	Vehicle	5%	10%	25%	Historical Positive Control
Stimulation Index	n/a	1.6	1.5	1.2	no data provided

C. Deviations - 1. The study report protocol states on page 28 that "Classical positive control substances are tested routinely in this laboratory in solvents (as per OECD guideline 429)." However, no historical control data are provided in the study. OECD Guideline 429 requires that a summary of results of the latest reliability check and historical positive control data for the testing laboratory be included in the study report. In addition, OPPTS guideline 870.2600 requires a concurrent positive control study.

2. The study report protocol states on page 28 that "If possible, the test will be conducted using the four highest concentrations listed of the following: 0.25, 0.5, 1.0, 2.5, 5, 10, 25, 50 and 100%." The doses tested in the study were 5, 10 and 25%. No explanation is provided as to why these particular doses were selected or why the screening test did not include higher doses.

3. The lymph nodes were pooled for each group. OPPTS Guideline 870.2600 specifies that counts should be recorded for each individual animal. Then the group mean DPM, along with an appropriate measure of inter-animal variability, should be calculated for each group.

D. Reviewer's Conclusions - Based on the results of this study, there is no indication that BYH 18636-Sulfonamide is a dermal sensitizer. However, due to the deviations, the study is classified as supplementary. While it does not satisfy the guideline requirement for an acceptable dermal sensitization study (OPPTS 870.2600, OECD 429) in the mouse, since the test substance is a metabolite and not technical grade material, TRB can accept it as supplementary data. This study may not be used to support registration of the test material.

1. **DP BARCODE:** D339738
2. **PC CODE:** 015804
3. **CURRENT DATE:** August 1, 2008
4. **TEST MATERIAL:** BYH 18636 Technical (94.6% thiencarbazone-methyl; Batch No. GELL 420-151-1; white powder)

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Bayer HealthCare AG AT03457, T 5077100 November14, 2006	47070205	LD_{50} > 2000 mg/kg bw males, females combined	III	A
Acute oral toxicity / rat Bayer HealthCare AG AT01452, T 5074266 September 15, 2004	47070119	LD_{50} > 2000 mg/kg bw males, females combined	III	A
Acute dermal toxicity / rat Bayer HealthCare AG AT01445, T 0074270 September 13, 2004	47070122	LD_{50} > 2000 mg/kg bw males, females combined	III	A
Acute inhalation toxicity / rat Bayer HealthCare AG AT01473, T2073309 September 20, 2004	47070123	LC_{50} > 2.018 mg/L males, females combined	IV	A
Primary eye irritation / rabbit Bayer HealthCare AG AT02437, T 4075381 September 27, 2005	47070124	No positive scores	IV	A
Primary dermal irritation / rabbit Bayer HealthCare AG AT01648, T 3073788/ December 1, 2004	47070203	Non-irritating	IV	A
Dermal sensitization / guinea pig Bayer HealthCare AG AT01388, T 5073096 August 9, 2004	47070204	Non- sensitizing	---	A

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived

METABOLITES:

TEST MATERIAL: BYH 18636 -carboxylic acid (purity 98.7%; Batch No. GSE 29091-1)

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Bayer HealthCare AG AT02902, T 3076352 March 14, 2006	47070121	LD_{50} > 2000 mg/kg bw (males and females)	III	A

TEST MATERIAL: BYH 18636 N-desmethyl (purity 98.7%; Batch No. GSE 29091-1)

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Bayer HealthCare AG AT03550, T 1077241 January 5, 2007	47070120	LD_{50} > 2000 mg/kg bw (males and females)	III	A

TEST MATERIAL: BYH 18636-sulfonamide (Purity: 99.0%; Batch No. CHZC007326; CAS No. 317815-81-9; light brown solid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Bayer HealthCare AG AT03432,T 8076771 July18, 2006	47070210	LD_{50} > 2000 mg/kg bw (males, females)	III	A
Acute dermal toxicity / rat Bayer HealthCare AG AT03211, T 9076772 July 18, 2006	47070211	LD_{50} > 2000 mg/kg bw (males and females)	III	A
Primary eye irritation / rabbit Bayer HealthCare AG AT03432, T 4076579 November 9, 2006	47070206	Conjunctival redness at 1 and 24 hours in 1/3 eyes.	III	A

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Primary dermal irritation / rabbit Bayer HealthCare AG AT03439, T 3076578 November 9, 2006	47070207	No dermal irritation was observed.	IV	A
Dermal sensitization / mouse Bayer CropScience SA 06367 February 28, 2007	47070209	Non-sensitizing	---	S